

### REMARKS

Reexamination and reconsideration is respectfully requested in light of the foregoing amendments to the claims and following remarks.

Applicant notes the Examiner's acknowledgment of Applicant's claim for foreign priority under 35 U.S.C. § 119 and receipt of the certified priority document. Claims 1-12, 19-27 and 31-33 are pending in this application.

Claims 13-18 and 28-30 have been canceled without prejudice or disclaimer. These claims had been withdrawn from consideration due to a restriction requirement. The claims are directed to a non-elected invention. Applicant reserves the right to file a divisional application for the non-elected invention set forth in the canceled claims.

New claims 31-33 have been added to recite that the H<sup>+</sup> hardly permeable membrane as set forth in independent claims 1, 2 and 19, respectively, is prepared from vacuole isolated from cells. Support for the new claims can be found at page 33, lines 27-28 of the specification.

### Rejection

Claims 1-12 and 19-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Clark et al. (U.S. Patent No. 6,951,744) (hereinafter "Clark") in view of the Zhen et al. publication (hereinafter "Zhen"). Applicant respectfully disagrees with the rejection and traverses as follows.

The Examiner alleges that Clark teaches, "detecting an extension product [in a polymerase chain reaction (PCR)] based on the digestion of pyrophosphate salt by (PPase)." See Final Office Action of March 28, 2006, page 3, lines 15-16. Furthermore, the Examiner erroneously states that Clark discloses "that the PPi release is measured as a primer extension

product produced, which is detected electronically.” *Id* at p. 4, lines 1-3. As evidence for this statement, the Examiner points to Figure 4, that depicts a picture of a gel displaying the results of a series of PCR reactions after completion of the reactions. Clark does not disclose measuring pyrophosphate (PPi).

As shown in Figure 1 below, Clark discloses that an extension reaction performed using PCR requires a template DNA, DNTPs (dATP, dTTP, dGTP, dCTP), a polymerase, and a magnesium ion. As the extension reaction proceeds, DNTPs are consumed, which produces pyrophosphatase (PPi) as byproduct. As one molecule of a base is added to a primer, one molecule of PPi is produced. As an example, if twelve DNTPs are consumed, twelve molecules of PPi are produced.

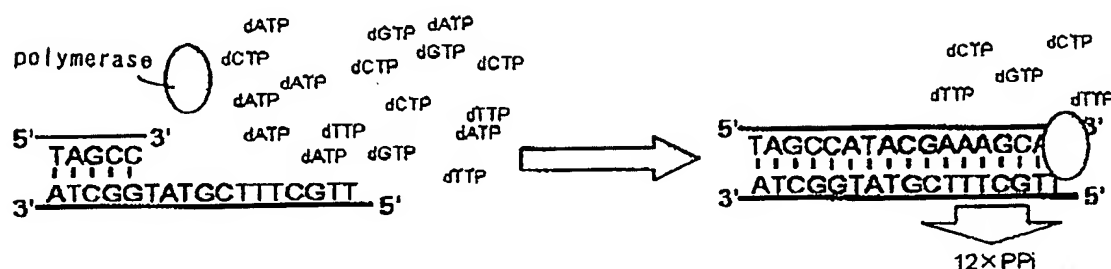


Figure 1. Schematic View of Primer Extension Reaction

There is no disclosure in Clark to teach or suggest using an increasing amount of PPi as a indicator of the progress of an extension reaction. More specifically, there is nothing in Clark that teaches or suggests a method of detecting an extension reaction or discriminating a base type based on the amount of PPi generated during the course of an extension reaction. Clark relates to a “Hot Start” methodology which involves proactively adding PPi to a PCR mixture so as to inhibit the primer extension reaction to avoid non-specific priming.

Even if the method claimed was taught or suggested by Clark, nothing in Clark discloses how one of skill in the art would go about detecting an increasing PPi concentration. The Examiner concedes that Clark does not teach the claimed permeable membrane having H<sup>+</sup>-pyrophosphatase feature of the invention. *Id* at p. 4, lines 6-9. It is the Examiner's position that this deficiency is overcome by Zhen.

Zhen teaches nothing about primer extension reactions in general, PCR in particular, let alone the generation of PPi during DNA synthesis. Zhen discloses a method in which a plant membrane associated H<sup>+</sup>-PPase hydrolyzes PPi and transports H<sup>+</sup> through the membrane. A pH sensitive pigment is then used to detect for the PPi. Zhen's invention is illustrated in Figure 2 below.

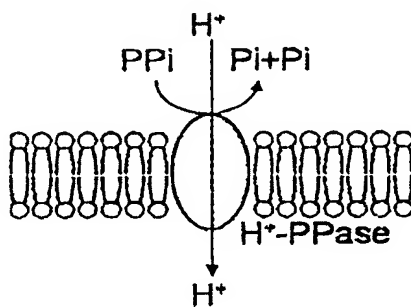


Figure 2. Function of H<sup>+</sup>-PPase

Clark and Zhen taken in combination would not render the invention obvious. the Examiner provides no cogent scientific explanation as to why such a person would have been motivated to modify Clark to incorporate the teachings of Zhen. The Examiner merely states that the skilled artisan would have the "expected advantage of developing a sensitive method for detecting base sequence of a target nucleic acid." The Examiner has not shown where or how

one could derive such an expectation in the cited references. As such, it is clear that the Examiner's rejection is based on improper hindsight reconstruction. As noted by our appellate court in *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971):

Any judgement [sic, judgment] on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper. [Underscoring added for emphasis.]

Clark discloses a PCR reaction, but he does not want to measure PPI. He uses PPI to control his reaction. Zhen on the other hand would measure PPI using the plant membrane and a pH sensitive pigment. In order for these references to be properly combined, the references must provide a teaching that would have motivated a person having ordinary skill in the art to modify Clark to include Zhen's means to measure PPI in a PCR reaction. Since Clark has no need to measure PPI and Zhen does not disclose that his membrane means can be used in PCR reactions, it appears that it was the Applicant's disclosure that provided the motivation to combine the references. Applicant's disclosure can never provide a basis for the motivation.

The Applicant has discovered that an increasing amount of PPI is a sensitive a indicator of the progress of an extension reaction and with the subject patent application, provides an efficient mechanism for its detection. This information is not taught or suggested by Clark and Zhen, taken alone or in combination. Therefore, the Examiner has improperly gleaned knowledge from the subject application to provide the nexis for combining Clark and Zhen to arrive at the claimed invention.

For all of the foregoing reasons, a person having ordinary skill in the art would not have found it is not possible to detect the progress of a primer extension reaction by measuring the concentration of pyrophoric acid (PPi) in a solution comprising dATP by using a H<sup>+</sup> hardly permeable membrane prepared from a vacuole isolated from a cell.

For all of the foregoing reasons, the Examiner has not presented a *prima facie* case of obviousness, and it is respectfully requested that the rejection claims 1-12 and 19-27 be reconsidered and withdrawn.

#### **New Claims 31-33**

As noted *supra*, new claims 31-33 have been added to recite that the H<sup>+</sup> hardly permeable membrane as set forth in independent claims 1, 2 and 19, respectively, is prepared from vacuole isolated from cells. This limitation is not taught or suggested by Clark or Zhen relied upon by the Examiner.

#### **Conclusion**

It is submitted that the claims 1-12, 19-27 and 31-33 are patentable over the teachings of the prior art relied upon by the Examiner. Accordingly, favorable reconsideration of the claims is requested in light of the preceding remarks. Allowance of the claims is courteously solicited.

If there are any outstanding issues that might be resolved by an interview or an Examiner's amendment, the Examiner is requested to call Applicants' attorney at the telephone number shown below.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due under 37 C.F.R. § 1.17 and due in

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connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read "Cameron Weiffenbach", written in a cursive style.

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